

EXPERIMENTAL STUDIES

The Thromboxane Receptor Antagonist SQ 30,741 Reduces Myocardial Infarct Size in Monkeys When Given During Reperfusion At a Threshold Dose for Improving Reflow During Thrombolysis

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The threshold dose of the selective thromboxane receptor antagonist SQ 30,741 for increasing reflow during thrombolysis was identified and then evaluated in a model of myocardial ischemia with reperfusion. In anesthetized cynomolgus monkeys, stenotic carotid arteries were occluded with a platelet-rich thrombus by electrical stimulation and recanalized with streptokinase (680 U/min intraarterially for 1 h) and heparin (200 U/kg + 120 U/h intravenously for 3 h). Concurrent administration of SQ 30,741 (2.1 mg/kg + 0.5 mg/kg per h intravenously for 3 h; $n = 4$) enhanced the extent of reflow 174% compared with saline solution ($n = 4$; $p < 0.05$) during the third hour, when lower doses were ineffective.

This threshold dose was tested in anesthetized African green monkeys subjected to 90 min of left circumflex coronary artery occlusion and 5 h of reperfusion. SQ 30,741 ($n = 8$) or saline solution ($n = 11$) was administered 2 min before reperfusion and continued throughout reper-

fusion. The heart was removed on termination of reperfusion and perfused in vitro with Evans blue and triphenyltetrazolium chloride dyes to stain tissue at risk and infarcted tissue, respectively. The percent of left ventricle at risk did not differ between saline- ($37 \pm 4\%$) and SQ 30,741-treated ($35 \pm 3\%$) monkeys. In contrast, infarcted tissue expressed as percent of the left ventricle at risk was less ($p < 0.01$) in monkeys receiving SQ 30,741 ($31 \pm 2\%$) than in those receiving saline solution ($49 \pm 5\%$).

This 36% reduction in infarct size occurred without significant differences between treatments in hemodynamic variables and myocardial blood flows (as assessed by radioactive microspheres) measured during control, occlusion and reperfusion intervals. Thus, a dose of SQ 30,741 that stabilizes reflow after thrombolysis also possesses anti-ischemic activity when administered only during coronary reperfusion in monkeys.

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It is now well established that thromboxane A_2 /prostaglandin H_2 receptor antagonists have a cardioprotective effect in vivo when administered during coronary reperfusion after an ischemic episode. This has been demonstrated by the capacity of structurally dissimilar thromboxane antagonists to reduce infarct size in dogs (1), cats (2) and rats (3) after a period of acute coronary artery occlusion and reperfusion. Overall, these studies suggest that thromboxane A_2 plays a deleterious role in experimental myocardial infarction. In addition to their anti-ischemic actions, thromboxane receptor antagonists are potent antiplatelet agents that generally have no direct hemodynamic effects (4). The demonstration

that thromboxane receptor antagonists improve reflow during thrombolysis in dogs (5,6) and monkeys (7) without altering systemic arterial pressure is consistent with this profile of activity.

The combination of an improved blood flow during revascularization and salvage of cardiac tissue during reperfusion could be efficacious in the treatment of acute myocardial infarction. Therefore, as a prelude to clinical investigation, it would be useful to identify a dose of a thromboxane receptor antagonist that possesses these complementary activities. The present study was designed to address this topic using a selective thromboxane receptor antagonist, SQ 30,741 (8,9), which has a short duration of action that could be advantageous in the critical care setting. All experiments were performed in anesthetized monkeys for a potentially closer comparison with humans. We first identified the threshold dose of SQ 30,741 required to improve reflow during streptokinase-induced thrombolysis. This dose of antagonist was then tested for reduction of myocardial infarct size when

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given only during reperfusion after 90 min of coronary artery occlusion.

Thrombolysis protocol. The experimental preparation is the same as that described previously (7). Seventeen cynomolgus male or female monkeys (*Macaca fascicularis*) (2.5 to 3.6 kg) were anesthetized with sodium pentobarbital (30 mg/kg intravenously), and the trachea was cannulated to maintain the airways patent. A PE-50 catheter was placed in each femoral vein, one for SQ 30,741 and saline infusions, the other for heparin infusion. A PE-90 catheter was placed in a femoral artery to record arterial blood pressure with use of a P23Db pressure transducer (Gould). The right carotid artery was isolated over a span of approximately 2 cm and a calibrated EP105 or EP106 electromagnetic flow probe (Carolina Medical Electronics) was attached to the vessel. A streptokinase infusion cannula (27 gauge hypodermic needle tip attached to tygon tubing) was inserted into the artery approximately 0.5 cm proximal to the flow probe. A stimulation electrode (5 mm tip of a 25 gauge hypodermic needle attached to a 30 gauge wire) was inserted 0.5 cm distal to the flow probe and adjusted to contact the intimal surface of the vessel. A 2 mm wide silver clip was placed over the vessel at the point of electrode insertion and adjusted so that carotid artery flow was reduced by approximately 25%. The clip was not manipulated further during the experiment, and any monkeys whose reflow exceeded that measured with the critical stenosis in place were not included in data analysis. Physiologic variables were monitored continuously on a model R611 recorder (Sensor Medics).

Occlusive thrombosis was produced by continuous stimulation with 100 μ A of anodal current. On thrombotic occlusion, the stimulation was terminated and the no-flow state was observed for 45 min before a 1 h intraarterial infusion of streptokinase (680 U/min) was started. Intravenous infusions of heparin (200 U/kg + 2 U/min) and administration of either vehicle (1 ml/h 0.9% saline solution, $n = 4$) or SQ 30,741 (1.0 mg/kg + 0.1 mg/kg per h, $n = 4$; 2.1 mg/kg + 0.25 mg/kg per h, $n = 5$; 2.1 mg/kg + 0.5 mg/kg per h, $n = 4$) was also begun and maintained for 3 h, at which time the experiment was terminated. Two monkeys were excluded because hyperemic flow made stability of the stenosis uncertain, but all others completed the protocol.

Acute myocardial infarction protocol. Twenty-one male or female African green monkeys (*Cercopithecus aethiops*) (3.1 to 7.0 kg) were anesthetized with sodium pentobarbital (30 mg/kg intravenously). PE-90 catheters were placed in a femoral vein for sodium pentobarbital and SQ 30,741 infusions and in a femoral artery to collect blood samples. A 5F SPC350 catheter pressure transducer (Millar Instruments) was inserted into a femoral artery to monitor arterial blood pressure. The trachea was cannulated, and respiration was maintained using a model 665 ventilator (Harvard Apparatus). The heart was exposed by a left thoracotomy at the fourth intercostal space, and the left circumflex coronary

artery was isolated proximal to the first marginal branch. A PE-90 catheter was placed into the left atrium for injection of ^{141}Ce -, ^{51}Cr -, ^{46}Sc - or ^{85}Sr -labeled microspheres (3M) in all but three monkeys. Myocardial blood flows were measured by a reference flow method (10). Arterial blood samples were obtained anaerobically before each microsphere injection, and blood gases were determined on a ABL3 analyzer (Radiometer). Respiration was adjusted to obtain an arterial Pco_2 of 35 to 40 mm Hg and $\text{Po}_2 > 60$ mm Hg. Arterial blood pressure, heart rate and lead II electrocardiogram were recorded continuously on a model 7D polygraph (Grass Medical Instruments).

When the preparation had stabilized microspheres were injected, and within 5 min the coronary artery was occluded with an atraumatic microvascular clamp. After 90 min of occlusion the clamp was released and reperfusion maintained for 5 h. Administration of either SQ 30,741 (2.1 mg/kg + 0.5 mg/kg per h, $n = 9$) or vehicle (6.7 ml + 0.16 ml/min saline solution, $n = 12$) began 2 min before reperfusion and was maintained throughout reperfusion. Microspheres were also injected after 45 min of occlusion and 1 h of reperfusion. At the end of the experiment the areas of the left ventricle at risk and infarcted areas were determined as described previously (11), except that the heart was removed and stained in vitro. Evans blue dye (0.5%) was perfused in a retrograde manner through the aorta and used to demarcate the area at risk (unstained tissue). The left circumflex coronary artery was cannulated with PE-50 tubing and perfused with a 1% solution of 2,3,5-triphenyltetrazolium chloride in phosphate-buffered saline solution to measure nonviable (unstained) and viable tissue (12). These dyes were each perfused at a pressure of 120 cm of H_2O for 5 min at 37%. The heart was cut transversely into five or six slices and both sides of each slice were traced manually onto a clear transparency. Areas were quantitated by computer-assisted planimetry. Tissue samples (0.5 to 0.8 g) for flows were taken from the subepicardium and subendocardium at the center of the ischemic area (most severe infarct and flow deprivation) and from a nonischemic section. Radioactivity was measured in tissue and reference blood samples with use of an Autogamma 8000 gamma counter (Beckman Instruments).

The person conducting the experiment and determining infarct size was unaware of the treatment administered. Cardioversion was performed in each of three monkeys with a single application of <20 J. One monkey died during coronary occlusion (saline group) and another was killed (SQ 30,741 group) because of inadequate oxygenation ($\text{Po}_2 < 50$ mm Hg), but all others completed the protocol.

Statistical analysis. Data were analyzed using a microcomputer statistics package (Systat). Comparisons between treatment groups were made by t test or, if appropriate, an analysis of variance. Data collected at multiple time points were subjected to analysis of variance with repeated mea-

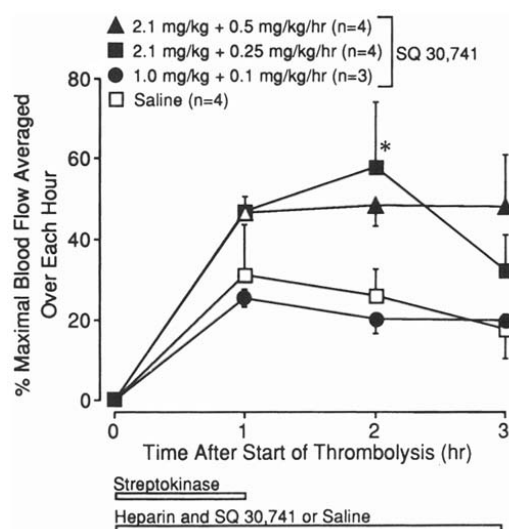


Figure 1. Thrombotically occluded carotid arteries of anesthetized cynomolgus monkeys ($n = 15$) were recanalized with streptokinase in the presence of heparin. The effect of either SQ 30,741 in three dose schedules or saline on reperfusion was determined using the blood flows averaged over each hour and expressed as percent maximal flow possible in the flow-limited stenotic vessel. * $p < 0.05$ for SQ 30,741 compared with saline. Data are mean values \pm SE.

tures. Mean differences within and between treatment groups were detected by contrasts. Analysis of covariance was used to add collateral flow and area at risk as covariants in testing for treatment effect on infarct size. A $p < 0.05$ (two-tailed) was required for statistical significance. All data in the text and figures are expressed as mean values \pm SE.

Results

Thrombolysis data. Thrombolytic reflow in the carotid artery was seen consistently during the 1 h streptokinase infusion (15 of 15 monkeys). The extent of reflow was determined by measuring area under the carotid blood flow trace over each hour and converting this to an average flow. These values were normalized as percent of the maximal value possible in the flow-limited vessel. Reflow measured in this manner was unaffected by any dose of SQ 30,741 (Fig. 1) during the hour of streptokinase infusion. During the third hour, only the 2.1 mg/kg loading dose plus the 0.5 mg/kg per h infusion of SQ 30,741 increased flow. The 2.1 mg/kg + 0.25 mg/kg per h dose was effective at 2 h, but its activity had deteriorated by hour 3. The 1 mg/kg + 0.1 mg/kg per h dose did not differ from the saline solution at any time.

All monkeys developed spontaneous cyclical flow variations consisting of periodic decreases and increases in carotid blood flow without alterations in arterial blood pressure. The peak and nadir flows detected during these responses were determined each hour to provide an index of reperfusion stability (Fig. 2). The treatment groups had similar peak flows both during and after streptokinase infu-

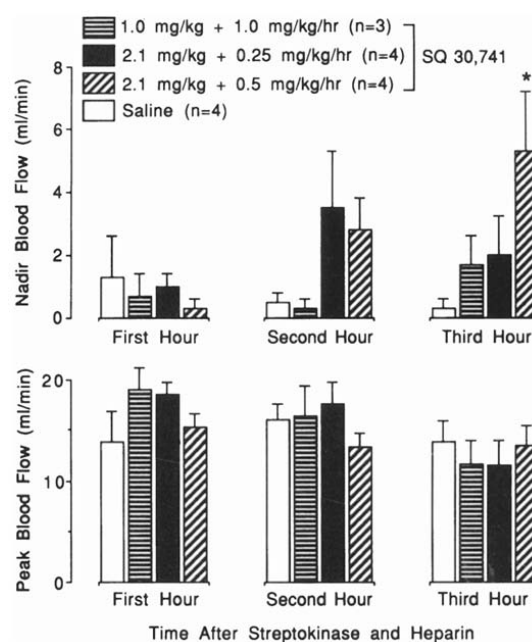


Figure 2. Streptokinase (1 h infusion) was administered along with heparin (3 h infusion) to reopen thrombotically occluded and stenotic carotid arteries of anesthetized cynomolgus monkeys. The effect of either SQ 30,741 or saline (3 h infusions) on the peak and nadir flows, which were observed during each hour was determined. * $p < 0.05$ for SQ 30,741 compared with saline. Data are mean values \pm SE.

sion. All animals exhibited a transient peak in carotid blood flow that at one time or another was close ($95 \pm 2\%$ overall) to the maximum possible in the stenotic vessel. The nadir blood flows did not differ during the first and second hours between treatment groups. There was a tendency for improvement in nadir flow during the second hour with the two highest doses of SQ 30,741, but statistical significance was not achieved. The 2.1 mg/kg + 0.5 mg/kg per h dose of SQ 30,741 increased nadir flow markedly only during the third hour, which contributed primarily to the enhanced average flow that was observed over this interval.

Reocclusions were observed after recanalization in all monkeys including those receiving the thromboxane receptor antagonist. Nevertheless, the average number of occlusive events was significantly reduced by the two highest doses of SQ 30,741 (Table 1).

Acute myocardial infarction data. Heart weight was similar in saline (29 ± 3 g) and SQ 30,741 (23 ± 1 g; $p = 0.10$)-treated monkeys. The area of the left ventricle at risk of infarction also did not differ between these treatment groups (Fig. 3). In contrast, infarct size expressed as a percent of the area of the left ventricle at risk was less ($p < 0.01$) with SQ 30,741 ($31 \pm 2\%$) than with saline solution ($49 \pm 5\%$). Infarct size expressed as percent of total left ventricle was also lower ($p < 0.05$) in monkeys receiving SQ 30,741 ($11 \pm 1\%$) compared with those receiving saline solution ($21 \pm 3\%$). The differences in infarct size between treatments were

Table 1. Effect of SQ 30,741 on Reocclusion During Streptokinase-Induced Thrombolysis in 15 Cynomolgus Monkeys

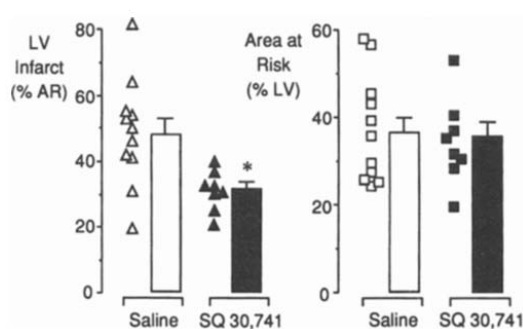
Treatment	Number of Reocclusions After Recanalization	Proportion of Animals Undergoing Reocclusion
Saline solution (1 ml + 1 ml/h)	6.5 ± 0.6	4/4
SQ 30,741 (1.0 mg/kg + 0.1 mg/kg per h)	5.3 ± 2.4	3/3
SQ 30,741 (2.1 mg/kg + 0.25 mg/kg per h)	2.8 ± 1.0*	4/4
SQ 30,741 (2.1 mg/kg + 0.5 mg/kg per h)	1.8 ± 0.6*	4/4

* $p < 0.05$ compared with saline solution by analysis of variance. Data are mean values ± SE.

also evident ($p < 0.05$) when an analysis of covariance was performed using blood flow measured during occlusion in the ischemic region (collateral flow) as a covariant. The typical nontransmural infarct observed in these monkeys was not usually localized to the subendocardium but tended to center in the midwall with additional involvement of either the subepicardium or subendocardium. Frequently, a narrow rim of epicardium remained viable in monkeys from both treatment groups.

Regional myocardial blood flows in the subepicardium and subendocardium did not differ between saline and SQ 30,741 groups at any time (Table 2). This was true for either the ischemic or nonischemic vascular beds. The collateral flow measured in the center of the ischemic zone during occlusion was low in all monkeys. Interestingly, the subepicardium appeared at greater risk than the subendocardium; however, this tendency did not reach statistical significance in either treatment group. Analysis of covariance revealed that left ventricular infarct size did not vary with collateral flow ($p = 0.601$), but did vary with area at risk ($p < 0.001$) and treatment group ($p < 0.05$). After 1 h of reperfusion,

Figure 3. Anesthetized African green monkeys were subjected to 90 min of left circumflex coronary artery occlusion and 5 h of reperfusion. Either SQ 30,741 (2.1 mg/kg + 0.5 mg/kg per h, intravenously) ($n = 8$) or saline solution ($n = 11$) was infused 2 min before and throughout reperfusion. The tissue at risk of infarction (AR) is expressed as percent of left ventricle (LV). The left ventricular infarct is expressed as percent of area at risk. * $p < 0.01$ for SQ 30,741 compared with saline solution. Data are individual and mean values ± SE.



subepicardial and subendocardial flows had recovered to essentially control values in both SQ 30,741- and saline-treated animals.

Analysis of hemodynamic data did not reveal any differences in arterial blood pressure, heart rate and double (rate-pressure) product between monkeys receiving SQ 30,741 or saline solution during the course of experiment (Table 3). Diastolic and systolic blood pressures were decreased equally and reproducibly in the saline ($-21 \pm 6\%$ and $-17 \pm 5\%$, respectively) and SQ 30,741 ($-21 \pm 6\%$ and $-17 \pm 4\%$, respectively) groups at 10 min after occlusion. On reperfusion, a further reduction in systolic blood pressure was observed only in saline-treated animals, but the actual values did not differ between treatments. There was a tendency for heart rate to increase with time so that the product of heart rate and mean arterial blood pressure did not deviate greatly over the duration of the experiment.

Discussion

Effects on thrombolysis. Size limitations precluded the use of the monkey coronary artery; however, blood flow in the carotid artery was similar to that found in the canine coronary artery favored by most other investigators who study thrombolysis in vivo. Of most importance, the stenotic carotid artery of the cynomolgus monkey is prone to the reduced blood flow and reocclusion observed in the canine coronary artery under similar conditions (5,13). We previously found (7) that antagonism of thromboxane receptors in monkeys primarily enhances reflow between 2 and 3 h after the start of thrombolysis. Enhancement of reflow during this interval was a primary objective in achieving our current goal of identifying a threshold dose of SQ 30,741 for adjunctive use with streptokinase. Continuous infusions were used in these experiments because of the short plasma half-life of SQ 30,741 in monkeys (9.5 ± 1.3 min, unpublished data).

The 2.1 mg/kg loading dose plus a 0.5 mg/kg per h intravenous infusion of SQ 30,741 increased blood flow by 174% during the third hour, which is similar to the effect obtained in our earlier study with 2 mg/kg + 2 mg/kg per h of SQ 30,741. There was also an increased nadir flow during the third hour and a reduction in the average number of reocclusions during the entire period of reperfusion in response to 2.1 mg/kg + 0.5 mg/kg per h of SQ 30,741. With a lower dose of 2.1 mg/kg + 0.25 mg/kg per h, the improvement in reflow was lost between 2 to 3 h, and therefore, this infusion rate was judged insufficient for sustained activity.

Maximal reflow was not influenced by any dose of SQ 30,741, an observation that is consistent with our previous findings (7). Carotid artery blood flow recovered to near the control stenosis-limited level in monkeys from both treatment groups, thus demonstrating the effectiveness of the thrombolytic regimen. The observation of intermittent reductions in reflow despite the presence of SQ 30,741 sug-

Table 2. Effect of SQ 30,741 on Regional Myocardial Blood Flows During Coronary Artery Occlusion and Reperfusion in African Green Monkeys

	Nonoccluded Region			Occluded Region		
	Control	45 min After Occlusion	60 min After Reperfusion	Control	45 min After Occlusion	60 min After Reperfusion
Subepicardium (ml/min per 100 g)						
Saline solution (n = 8 to 9)	103 ± 8	105 ± 12	119 ± 15	111 ± 10	1 ± 1*	170 ± 23
SQ 30,741 (n = 5 to 7)	105 ± 16	133 ± 28	133 ± 37	100 ± 13	2 ± 1*	141 ± 37
Subendocardium (ml/min per 100 g)						
Saline (n = 8 to 9)	120 ± 12	126 ± 15	155 ± 19	117 ± 10	5 ± 3*	116 ± 34
SQ 30,741 (n = 5 to 7)	117 ± 8	121 ± 17	119 ± 21	130 ± 21	6 ± 3*	112 ± 32

*p < 0.01 compared with respective control by analysis of variance with repeated measures. There were no significant differences between saline and SQ 30,741. All data are mean values ± SE.

gests that mediators other than thromboxane maintain a proaggregatory or vasospastic stimulus. Another possibility is that incomplete thrombolysis limited the restoration of vessel patency. However, in the original canine version of this model (13), similar cyclical flow reductions were not altered by increasing the streptokinase dose after reflow, a finding that suggests that these responses are not primarily attributable to insufficient thrombolysis. Mickelson et al. (14) found that similar responses in stenotic arteries that had been injured by electrical current were associated with platelet accumulation and could be abolished by monoclonal antibodies to the platelet GPIIb/IIIa receptor. Others have reported improved efficacy in sustaining reflow in recanalized arteries by combining antagonists of thromboxane and serotonin receptors (6).

The time to reperfusion is one important variable that was not analyzed because of the large variability encountered relative to the number of animals studied. To better detect effects on lysis time, we combined present and

previous data (ref. 7 and unpublished observations) for monkeys treated with the same amount of streptokinase plus heparin and either vehicle (n = 20) or a loading dose of 2 mg/kg of SQ 30,741 (n = 17). In this analysis there was a tendency for shorter times to reperfusion in the presence of SQ 30,741, but this effect did not attain statistical significance (28 ± 5 and 19 ± 3 min, respectively; p = 0.126). Golino et al. (6) also did not detect acceleration in the time to reperfusion with a tissue plasminogen activator in canine coronary arteries using a different thromboxane receptor antagonist unless a serotonergic antagonist was coadministered. In contrast, Shebuski et al (5) reported that yet another thromboxane receptor antagonist reduced the time for clot lysis with a tissue plasminogen activator in canine coronary arteries by about 65%. Differences in the species, size and type of artery, method of inducing thrombosis and thrombolytic agent could have contributed to these discrepant results. Overall, the most reproducible effect of thromboxane receptor antagonism

Table 3. Effect of SQ 30,741 on Hemodynamic Variables During Coronary Artery Occlusion and Reperfusion in 19 African Green Monkeys

	Control	Occlusion			Reperfusion			
		10 min	45 min	85 min	10 min	1 h	2 h	5 h
Systolic blood pressure (mm Hg)								
Saline (n = 11)	106 ± 4	88 ± 7*	85 ± 6*	86 ± 5*	76 ± 5†	86 ± 5	85 ± 3	82 ± 3
SQ 30,741 (n = 8)	95 ± 6	80 ± 8*	90 ± 9	89 ± 6	81 ± 6	89 ± 4	96 ± 6	90 ± 6
Diastolic blood pressure (mm Hg)								
Saline (n = 11)	83 ± 3	66 ± 7*	64 ± 8*	65 ± 8*	56 ± 5†	66 ± 5	67 ± 4	63 ± 3
SQ 30,741 (n = 8)	78 ± 5	63 ± 8*	70 ± 6	68 ± 5	61 ± 6	68 ± 4	75 ± 6	66 ± 6
Heart rate (beats/min)								
Saline (n = 11)	161 ± 30	116 ± 10	129 ± 11	135 ± 11	137 ± 9	147 ± 8	15 ± 11	172 ± 10
SQ 30,741 (n = 8)	148 ± 9	137 ± 16	145 ± 18	151 ± 18	154 ± 12	17 ± 13	176 ± 11	173 ± 10
Rate-pressure product (beats/min-mm Hg) × 10 ³								
Saline solution (n = 11)	14 ± 2	9 ± 1	10 ± 2	10 ± 1	9 ± 1	11 ± 1	11 ± 1	12 ± 1
SQ 30,741 (n = 8)	12 ± 1	10 ± 2	11 ± 2	11 ± 2	11 ± 1	11 ± 1	14 ± 1	13 ± 1

*p < 0.01 compared with control and †p < 0.01 compared with 85 min occlusion by analysis of variance with repeated measures. There were no significant differences between saline solution and SQ 30,741. All data are mean values ± SE.

among various studies has been mitigation of the low flow state or reocclusion, or both subsequent to thrombolysis.

Effects on acute myocardial infarction. Experiments were performed in African green instead of cynomolgus monkeys because of their increased size and availability. The threshold dose of SQ 30,741 for increasing thrombolytic reflow was clearly efficacious against reperfusion injury. Infarct size expressed as percent of the left ventricle at risk was reduced by 36% when SQ 30,741 was administered immediately before and throughout reperfusion. A comparable 33% reduction in this variable was observed previously (11) when SQ 30,741 was given only during reperfusion in dogs exposed to the same durations of ischemia and reperfusion. Saline-treated animals in both studies had 49% of the left ventricle at risk infarcted, although a slightly higher proportion of the left ventricle was placed at risk by circumflex artery occlusion in dogs (approximately 47%) compared with monkeys (approximately 36%). These results demonstrate that SQ 30,741 is cardioprotective in both monkeys and dogs, despite the potential for interspecies variability in the production or reactivity to thromboxane, or both (15,16).

SQ 30,741 did not alter arterial blood pressure, heart rate or the rate-pressure product any any time, a fact that argues against a primary contribution of hemodynamic factors in the observed treatment effects on infarct size. There were also no differences in myocardial blood flow between SQ 30,741- and saline-treated monkeys during the course of the experiment. In both treatment groups subepicardial and subendocardial collateral flows were very low in the central ischemic zone. Ischemia of this severity has also been described in baboons (17) and is in contrast to the relatively greater collateral flows that we have routinely observed in dogs (1,11,18). Because collateral flows were uniformly low, they neither correlated with infarct size nor altered the interpretation of drug effects on infarct size. This was not the situation for area at risk, where a high correlation with infarct size was evident in both treatment groups. The equal recovery of myocardial flows after 1 h of reperfusion in monkeys treated with either SQ 30,741 or saline solution agrees with previous findings in dogs treated during reperfusion only (11). Administration of SQ 30,741 during both occlusion and reperfusion has consistently improved subendocardial flow during early reperfusion, indicating some additional benefit in treating before reperfusion (11,18).

Mechanisms. The mechanism responsible for the myocardial sparing activity was not addressed in the current study. It is unlikely that limitation of thromboxane production is important because ischemia-related increases in thromboxane production during permanent coronary artery ligation were unaffected by cardioprotective doses of two structurally dissimilar thromboxane receptor antagonists (19,20). The most obvious mechanism of action would include blockade of the deleterious responses to thromboxane

receptor activation, such as vasospasm, platelet activation or cytotoxicity (21,22). The exact response, the type of cells participating and the source of thromboxane remain unclear. Recent attention has been given (23) to inflammatory reactions mounted by blood elements, especially neutrophils, in which free radical generation may participate in reperfusion-associated myocardial injury. Thromboxane receptor antagonists reduce neutrophil infiltration into infarcted myocardium during coronary occlusion with (2) or without (19) reperfusion. This effect may represent either a direct action on neutrophils or a diminished stimulus for infiltration secondary to reduced tissue damage by other mechanisms. The ability of the thromboxane antagonist BM 13,505 to inhibit neutrophil activation in whole blood *ex vivo* (24), and also neutrophil infiltration into rat hindpaws *in vivo* (2), suggests a more direct role for thromboxane in neutrophil function.

Summary and clinical utility. We have demonstrated that SQ 30,741 can be given at a dose that increases reflow during thrombolysis and also salvages myocardial tissue after acute ischemia and reperfusion. The combination of anti-ischemic and thrombolytic-enhancing activities in a single compound offers the potential advantage of limiting drug interactions. Descriptions of platelet activation during thrombolytic use in experimental animals (25) and in humans (26) certainly support the platelet inhibition as a desirable goal. Unfortunately, this activity may also accentuate bleeding and, therefore, a short-acting compound like SQ 30,741 might offer the additional advantage of better hemostatic control.

Regarding the anti-ischemic effects of SQ 30,741, we have not determined the critical duration of treatment necessary to reduce ultimate infarct size in monkeys. However, in a previous study (11) SQ 30,741 was given to dogs during occlusion and 4 h of reperfusion and reduced infarct size measured after 24 h. This information, combined with the observation that thromboxane receptor antagonists salvage cardiac tissue after 48 h of complete coronary artery occlusion (20), suggests that thromboxane receptor blockade can result in long-lasting cardioprotective effects.

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